DECLARATION OF THOMAS D. MADDEN, PH.D.

I, Thomas D. Madden, Ph.D., declare as follows:

1. I currently hold the position of Senior Director, Technology Development & Licensing, at Inex Pharmaceuticals Corp. ("INEX"), located in Burnaby, British Columbia, Canada, an assignee of U.S. Patent Application No. 10/782,738, entitled "Compositions and Methods for Treating Lymphoma."

2. I have read and am familiar with the above-identified patent application and the Office Action mailed July 20, 2006 with respect to this application. In this Office Action, the Examiner suggests that one would be motivated to produce a kit for the preparation of liposome-encapsulated vincristine having the three components recited in the instant application, in light of the teachings of Webb (U.S. Patent No. 5,741,516), alone or in combination with Mehlhorn (U.S. Patent No. 5,762,957). I submit this Declaration as evidence that the kits claimed in the instant application, which comprise three specific components that are combined to produce liposome-encapsulated vinca alkaloids, are not obvious in light of these references. The presently claimed kits provide surprising and unexpected advantages, including increased drug stability, which would not have been recognized prior to the filing of the instant application. In addition, I submit that the skilled artisan would not have been motivated to produce the liposomal vincristine kits claimed in the above-identified patent application in light of these references.

3. I strongly disagree with the Examiner's position that the skilled artisan would be motivated by Webb, alone or in combination with Mehlhorn, to produce a kit containing liposomes and drug separately. The kit of the present invention is used to prepare a pharmaceutical composition for administration to a patient. In the context of pharmaceutical compositions, a kit that requires the user to prepare the formulation is much less commercially attractive than a "ready-to-use" format, such as those described in Webb. Such a kit requires additional work and equipment on the part of the user, and,

if not used correctly, it could potentially introduce variability in the final composition, which could present safety and efficacy concerns.

4. In the case of a liposomal pharmaceutical, a product format consisting of drug-loaded liposomes suitable for direct patient administration or administration after constitution of a lyophilized powder, is greatly preferred compared to a kit format wherein the drug, *e.g.*, vincristine, must be loaded into the liposomes prior to patient administration. Loading immediately prior to use requires both additional equipment and time on the part of the physician or hospital. For example, optimal loading of vincristine into sphingomyelin:cholesterol liposomes occurs when the drug, liposomes, and sodium phosphate buffer are combined and incubated at 63-65°C for 10 minutes. The sphingomyelin:cholesterol bilayer is highly ordered and only at elevated temperatures is vincristine able to cross the bilayer and accumulate in the aqueous interior. If the incubation is conducted at temperatures below about 55°C, loading efficiency is very poor with essentially no drug loading observed at 40°C or below (Figure 1). Furthermore, if the incubation time is less than 10 minutes, loading may be incomplete. For example, when the mixture is incubated at 60°C for 5 minutes, more than 15% of the vincristine is unencapsulated. Finally, at higher incubation temperatures and longer incubation times, the amount of vincristine degradation is increased. Accordingly, constitution of the final liposomal pharmaceutical requires additional equipment and manpower on the part of the end-user, including, *e.g.*, a water bath and a technician or pharmacist to conduct the loading procedure, and would, therefore, be less desirable than using a preloaded liposomal drug formulation.

5. In addition, the skilled artisan would understand that any error during constitution of liposome-encapsulated vinca alkaloids could result in reduced efficacy of the resulting liposomal drug formulation or even undesired side-effects. For example, vincristine is a neurotoxic agent, but this toxicity is greatly ameliorated by encapsulation in sphingomyelin:cholesterol liposomes. Accordingly, liposomal vincristine is administered to patients at much higher doses and frequency than the free drug. Specifically, conventional (free) vincristine is typically administered at a dose of 1.4

mg/m^2, usually with a dose cap of 2 mg (regardless of patient body surface area), every 3 weeks. In contrast, liposomal vincristine is typically administered at 2.0 mg/m^2, without dose capping, every 2 weeks. For the treatment of acute leukemia patients, doses up to 2.4 mg/m^2, weekly, are used. Therefore, if an error occurred during constitution of liposomal vincristine, such that the drug were not fully loaded, a potentially toxic dose of free vincristine might be administered to the patient. Further, incomplete drug loading would also reduce the efficacy of the product, potentially resulting in a poorer clinical outcome for the patient. Therefore, the end-user would prefer to use a pre-loading liposomal formulation to eliminate any risk of reduced efficacy or possible toxicity.

6. The above considerations would be well-known to someone of ordinary skill in the art and would provide a strong prejudice against adoption of a kit format requiring constitution prior to use, in the absence of a compelling need or motivation. Such a need or motivation was not recognized in the art prior to the filing of the instant application. As noted in my Declaration submitted May 23, 2006, the fully loaded liposomal vincristine formulations disclosed in Webb, which are stated to provide stable drug retention in a chemically stable lipsomal carrier, would appear to be an ideal product presentation. Unrecognized by Webb, however, the chemical stability of vincristine within the liposomal interior greatly limits the acceptable shelf-life for such a loaded formulation. Specifically, the levels of vincristine degradents within the loaded liposomes exceed the USP requirements within less than 6 months of manufacture. As shown in Table 1, vincristine encapsulated in sphingomyelin:cholesterol liposomes (as described by Webb) undergoes significant degradation in the acidic liposome interior. While the liposomal product has an initial vincrintine sulfate purity of greater than about 98%, after 24 week storage at 2-8°C this has decreased to less than 95% (duplicate sample).

Table 1. Stability of Vincristine Sulfate Encapsulated in Sphingomyelin:Cholesterol Liposomes at 2-8°C.

Parameter	**Stability Timepoints (weeks)**					
	0	4	8	12	24	36
Vincristine Sulfate Purity (duplicates)	99.0/97.9	97.9/98.0	97.5/97.3	96.3/96.3	95.2/93.4	89.1/89.4

Such a short shelf-life is unsuitable for a pharmaceutical product. Accordingly, the adoption of a kit format for loading prior to use is necessary, despite being less desirable from a commercial and clinical perspective. Studies conducted by INEX confirm that the kit format for liposomal vincristine provides for a shelf-life of 2 years.

7. The Examiner has also suggested that someone of ordinary skill in the art would be motivated to provide empty liposomes and vincristine separately because this would allow the user to vary the amount of encapsulated vincristine. I strongly disagree with this suggestion. The sale and use of pharmaceutical products is regulated by the United States Food and Drug Administration, as set forth in Section 21 of the Code of Federal Regulations. All pharmaceutical products must meet strict specifications that define product parameters controlling safety and efficacy. In the case of liposomal drugs, these specifications include drug concentration, lipid concentration, and the drug:lipid ratio. Since the drug:lipid ratio would be expected to affect both drug pharmacokinetics and pharmacodynamics, this parameter is strictly defined for each product. Accordingly, someone of ordinary skill in the art would understand it to be both irresponsible and illegal to vary the amount of encapsulated drug in a liposomal drug product intended for clinical use and would not be motivated to do so. It should also be noted that product specifications for a liposomal pharmaceutical must include tight control over the level of unencapsulated drug (see paragraphs 4 and 5 above) consistent with the need to ensure product safety and efficacy.

8. With respect to Mehlhorn, I submit that Mehlhorn also fails to motivate the skilled artisan to produce a kit for preparing liposomal vinca alkaloids having the three components presently claimed. Mehlhorn requires that the drug be included in either the vial containing the liposomes or the vial containing the buffer. In contrast, in the kits claimed in the instant application, the drug is provided in a third vial.

9. In addition, the kit formats disclosed by Mehlhorn are unsuitable to provide a liposomal vincristine product with an acceptable shelf-life. Vincristine is unstable in alkaline solutions and hence would be rapidly degraded in the buffer vial.

Further, vincristine is known to exhibit optimal stability at pH 3.5-5.5 (Vendrig et al. International Journal of Pharmaceutics, 50 (1989) 189-196). Accordingly, if, for the purpose of argument, it was considered that Mehlhorn provided a motivation to provide liposomal vincristine in a kit format, it would have been obvious to include the drug within the liposome vial (as suggested by Mehlhorn) as the liposomes are suspended in citrate buffer pH 4.0. What was not known in the art prior to the filing of the instant application, is that in this citrate buffer, vincristine would be degraded at the same rate as if encapsulated in the liposomes - as the aqueous environment is the same. Accordingly, such a kit format would have the same limited shelf-life as the fully loaded liposomes. It is only by providing the vincristine sulfate in a separate vial, in a solution suited to drug stability, that a commercially acceptable shelf-life is achieved. Thus, the presently claimed kits, which comprise three components: (1) liposomes; (2) buffer; and (3) drug in a solution suited to drug stability; provide unexpected advantages over the kit formats described by Mehlhorn.

10. In summary, Webb discloses liposomal vincristine formulations that are claimed to show excellent stability (drug retention and phospholipid integrity) as the fully loaded formulation. Webb does not suggest kits comprising separate vials of liposomes and vinca alkaloid for preparation prior to use (as presently claimed), and, in fact, such a kit would run counter to the disclosure in Webb. Taken together with the skilled artisan's clear understanding that constitution of a liposomal kit within a hospital environment would be time-consuming, laborious, and carry inherent risk of error, there exists a strong prejudice against adoption of such a kit format. It is only the applicants who have recognized the requirement to create such a kit in order to address a drug stability problem unanticipated by Webb. In doing so, applicants have adopted a kit format that is uniquely suited to liposomal vinca alkaloids, *e.g.*, vincristine, and is clearly distinct from the kits disclosed by Mehlhorn.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements

and the like so made are punishable by fine or imprisonment, or both, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Date October 20th 2006

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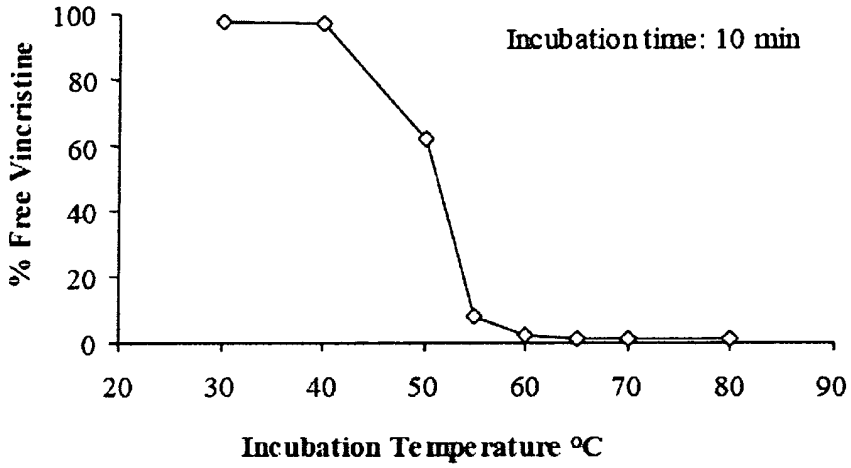

Figure 1